DALTON COMMUNICATION

Aromatic C–F activation at Ni in the presence of a carbon–chlorine bond: the nickel mediated synthesis of new pyrimidines †

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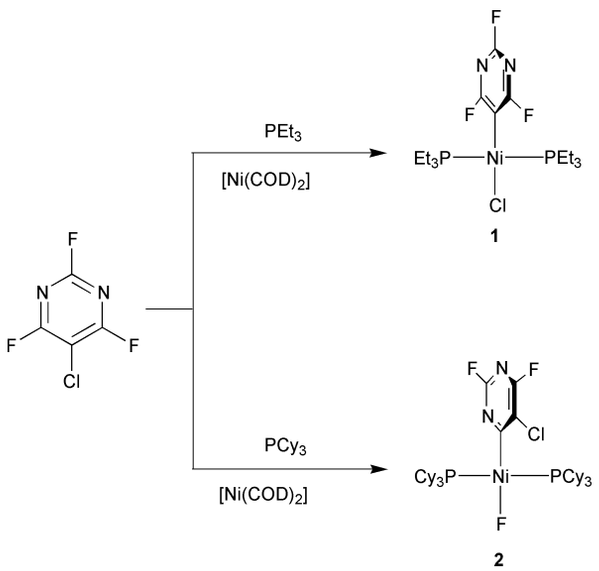
Treatment of $[Ni(COD)_2]/PCy_3$ with 5-chloro-2,4,6-trifluoropyrimidine affords the C–F activation product *trans*-$[NiF(4\text{-}C_4N_2ClF_2)(PCy_3)_2]$ 2, which reacts with iodine to form 5-chloro-2,6-difluoro-4-iodo-pyrimidine 5.

Several methods have been described for the activation of carbon–fluorine bonds of fluoroaromatic compounds by reaction at transition metal centres.[1] Catalytic C–F activation has also become a reality.[2–4] However, the formation of new organofluorine compounds *via* C–F activation, followed by functionalisation within the coordination sphere of the metal is still little developed.[3–6] Nevertheless, the activation of a C–F bond in pentafluoropyridine, 2,3,5,6-tetrafluoropyridine or 2,4,6-trifluoropyrimidine at a nickel centre can be used as a remarkable approach to obtain fluorinated derivatives which are otherwise inaccessible.[4,6–8] While C–F activation at nickel is selective over C–H activation,[2,4,9,10] the activation of a C–F bond in the presence of a C–Cl bond in the same ring has never been observed. Crespo *et al.* reported the C–F activation of the imine $(C_6F_5)CH{=}NCH_2(2\text{-}ClC_6H_4)$ at a Pt(II) centre, but with the C–F and C–Cl bond on different rings.[11] In this communication we describe (1) the activation of a C–F bond in the presence of a much weaker C–Cl bond in the same aromatic ring, (2) that the chemospecificity of the activation of a C–X bond (X = F, Cl) in 5-chloro-2,4,6-trifluoropyrimidine by $[Ni(COD)_2]/PR_3$ (R = Et, Cy; COD = cycloocta-1,5-diene) is controlled by the size of the phosphine, (3) the nickel-mediated synthesis of new fluorinated pyrimidines by C–F activation.

The stepwise treatment of $[Ni(COD)_2]$ with PEt_3 and 5-chloro-2,4,6-trifluoropyrimidine in hexane solution at room temperature results in the formation of *trans*-$[NiCl(5\text{-}C_4N_2F_3)(PEt_3)_2]$ **1**, which was crystallised at −20 °C (Scheme 1).‡ The isolated yield of 20% was limited principally by the extreme solubility of the product. However, there was a minor amount (5%) of a yellow solid, insoluble in all common solvents, which could not, as yet, be identified. The ^{19}F NMR spectrum of **1** shows two resonances at δ −37.77 and −55.72 with a ratio of 2 : 1 revealing the presence of the trifluoropyrimidyl group. The observed preference for C–Cl activation is fully consistent with comparable reactions of chloropentafluorobenzene and 3,5-dichlorotetrafluoropyridine, which are described in the literature.[9]

On using PCy_3 instead of PEt_3 exclusive activation of the C–F bond takes place. Treatment of $[Ni(COD)_2]$ with PCy_3 in the presence of 5-chloro-2,4,6-trifluoropyrimidine results in the formation of *trans*-$[NiF(4\text{-}C_4N_2ClF_2)(PCy_3)_2]$ **2**.‡ The ^{31}P and ^{19}F NMR spectrum of the reaction solution reveals the presence of a minor product (18%), which was assigned as *trans*-$[NiCl(4\text{-}C_4N_2ClF_2)(PCy_3)_2]$ **3**.‡ However, after recrystallisation we obtained a pure sample of **2** in moderate yield (34%). The ^{19}F NMR spectrum of **2** exhibits a triplet at δ −377.56 (J_{PF} 40 Hz) characteristic of the metal fluoride and two further resonances at δ −49.86 and −73.67 with a 1 : 1 ratio revealing the presence of a difluoropyrimidyl group.[4,8–10] The ^{31}P NMR spectrum displays a doublet resonance at δ 19.65 (J_{PF} 39 Hz) for the two equivalent phosphorus nuclei coupled to the metal-bound fluorine.



Scheme 1 Reactivity of $[Ni(COD)_2]$ towards 5-chloro-2,4,6-trifluoropyrimidine.

The formation of compound **3** can be explained by a reaction of **2** with free 5-chloro-2,4,6-trifluoropyrimidine. Indeed, treatment of a solution of **2** with the organic substrate affords complex **3**. A comparable substitution of a metal-bound fluoride by a chloro ligand using chloropentafluorobenzene has been described at a rhodium centre.[12] Complex **3** can also be synthesised by reaction of **2** with NaCl (Scheme 2).

Complex **2** was crystallised at −20 °C from hexane. The structure was determined by X-ray diffraction at low temperature (Fig. 1).§ Despite a rotational disorder of the aromatic ring in **2** (62 : 38) the structure provides useful data.The Ni–F bond of 1.845(2) Å is comparable to the distance found in *trans*-$[NiF(2\text{-}C_5NF_3H)(PEt_3)_2]$ [1.856(2) Å].[9] The distance found for the Ni–C bond in **2** [1.828(8) Å, 1.863(12) Å] is in the same range as the values found in **1** [1.8849(13) Å] and *trans*-$[NiF(2\text{-}C_5NF_3H)(PEt_3)_2]$ [1.869(4) Å].†[9]

We believe that a precoordination of the aromatic system at the nickel centre, *via* a nitrogen atom or in an η^2 mode, is a crucial step in the activation of a C–X bond in 5-chloro-2,4,6-trifluoropyrimidine. Similar intermediates have been discussed in the C–F activation of hexafluorobenzene, octafluoronaphthalene and pentafluoropyridine at $Ni(PEt_3)_2$.[4,9,10,13] It has been proposed that these reactions proceed by a concerted oxidative addition mechanism. The observed chemospecificity in the formation of **1** and **2** might therefore be attributed to different intermediates or, more likely, different transition states.[13,14] Although there is a small difference in the electronic properties of PEt_3 and PCy_3 at nickel, we believe that the chemospecificity is determined by steric factors.[15] However,

† Electronic supplementary information (ESI) available: synthesis details for compounds **1**–**3** and crystal data for **1**. See http://www.rsc.org/suppdata/dt/b1/b110128e/

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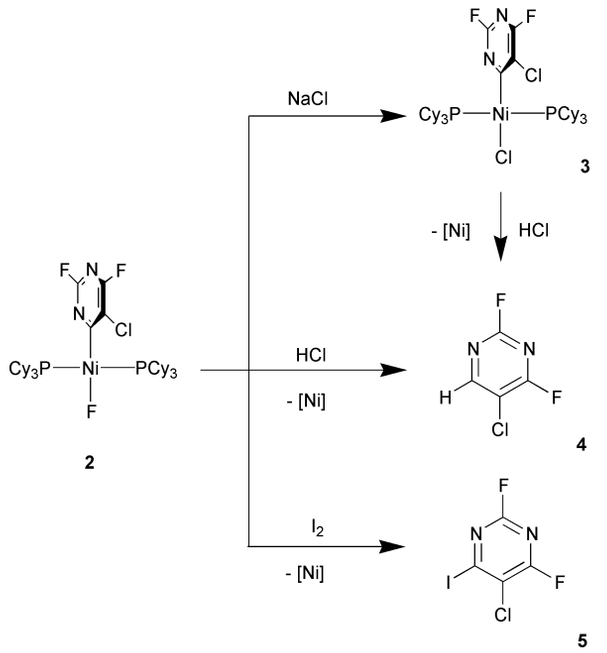

Scheme 2 Reactivity of **2**.

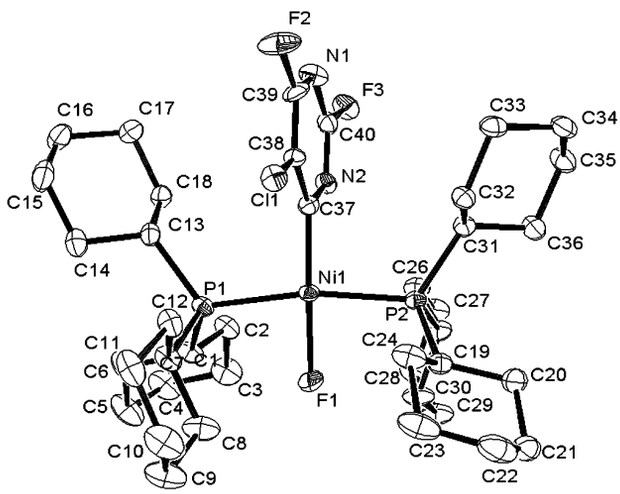

Fig. 1 An ORTEP[18] diagram of **2**. Ellipsoids are drawn at the 50% probability level. Note that the rotational disorder (62 : 38) about Cl(1), N(1), N(2), F(2), F(3) and C(37)–C(40) leads to average locations across the pyrimidyl ring. The two rotamers have identical bond distances within 3σ. Data for the second rotamer are marked by a #. Selected bond lengths (Å) and angles (°): Ni(1)–F(1) 1.845 (2), Ni(1)–C(37) 1.828(8), Ni(1)–C(37#) 1.863(12), N(2)–C(37) 1.362(7), N(2)–C(40) 1.307(6), N(1)–C(40) 1.297(7), N(1)–C(39) 1.30(2), C(37)–C(38) 1.398(7), C(38)–C(39) 1.40(2), Cl(1)–C(38) 1.713(4), F(2)–C(39) 1.31(2), F(3)–C(40) 1.344(5); C(37)–Ni(1)–F(1) 172.98(18), C(37#)–Ni(1)–F(1) 170.4(3), P(1)–Ni(1)–P(2) 168.74(2).

we also cannot exclude that instead of a concerted oxidative addition mechanism an electron transfer process precedes the activation of the C–X bond.[16] Further mechanistic investigations are under way.

Treatment of **2** or **3** with an excess HCl in C_6D_6–diethyl ether affords, after distillation under vacuum, a solution of 5-chloro-2,4-difluoropyrimidine **4** (Scheme 2).¶ The reaction of **2** with iodine in C_6D_6 yields a solution of 5-chloro-2,6-difluoro-4-iodopyrimidine **5**.¶ The reactions are quantitative according to the NMR spectra. We have found no previous description of compound **4** or **5**. Fluorinated pyrimidines are of general interest as building blocks in agrochemicals, dyes and because of their antitumor activity.[6,17]

In conclusion, we have shown the first activation of an aromatic carbon–fluorine bond at a metal centre in the presence of a C–Cl bond in the same ring. Comparable C–F activation reactions at nickel with a unique regioselectivity and a preference for C–F over C–H activation have been studied before.[8–10] We have now demonstrated that the scope of these reactions can be expanded to the activation of a carbon–fluorine bond in 5-chloro-2,4,6-trifluoropyrimidine using a sterically more hindered phosphine. The described reaction provides an unusual entry to new fluoropyrimidines bearing three different substituents by selective replacement of one fluorine atom at the already functionalised heterocycle.

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Notes and references

‡ Selected data for **1**, **2** and **3**. **1**: (Found: C, 40.84; H, 6.53; N, 5.99%. $C_{16}H_{30}ClF_3N_2NiP_2$ requires: C, 41.46; H, 6.52; N, 6.04%). ^{31}P NMR (202.5 MHz, C_6D_6, 300 K): δ 15.83 (s). ^{19}F NMR (470.4 MHz, C_6D_6, 300 K): δ −37.77 (s, br, 2 F), −55.72 (s, br, 1 F). **2**: (Found: C, 60.50; H, 8.35; N, 3.59%. $C_{40}H_{66}ClF_3N_2NiP_2$ requires: C, 60.97; H, 8.44; N, 3.55%). ^{31}P NMR (202.5 MHz, C_6D_6, 300 K): δ 19.65 (d, J_{PF} 39 Hz). ^{19}F NMR (470.4 MHz, C_6D_6, 300 K): δ −49.86 (s, 1 F), −73.67 (s, 1 F), −377.56 (t, J_{PF} 40 Hz, 1 F). **3**: (Found: C, 59.92; H, 8.70; N, 3.10%. $C_{40}H_{66}Cl_2F_2N_2NiP_2$ requires: C, 59.72; H, 8.27; N, 3.48%). ^{31}P NMR (202.4 MHz, C_6D_6, 300 K): δ 15.67 (s). ^{19}F NMR (470.4 MHz, C_6D_6, 300 K): δ −48.91 (s, 1 F), −73.77 (s, 1 F).

§ Crystal data for **2**: $C_{40}H_{66}ClF_3N_2NiP_2$, M = 788.05, monoclinic, space group $P21/n$, a = 13.8320(10), b = 20.2110(15), c = 14.5510(10) Å, β = 90.459(6)°, U = 4067.7(5) Å^3, T = 100 K, μ(Mo-Kα) = 0.665 mm^{-1}, Z = 4, D_c = 1.287 g cm^{-3}, 28171 reflections measured, 9114 unique (R_{int} = 0.0409). The disorder of the pyrimidyl ligand on two positions was refined to an occupancy of 62 : 38. Final R_1, wR_2 values on all data 0.06457, 0.0942. R_1, wR_2 values on [$I_o > 2\sigma(I_o)$, 7325 reflections] data 0.0449, 0.0890. CCDC reference number 173741. See http://www.rsc.org/suppdata/dt/b1/b110128e/ for crystallographic data in CIF or other electronic format.

¶ Selected spectroscopic data for **4** and **5**. **4**: NMR (C_6D_6, 300 K): ^{1}H (500.1 MHz): δ 7.37 (d, br, J_{FH} 11 Hz, CH), ^{19}F (470.4 MHz): δ −45.69 (s, br, 1 F), −59.15 (s, br, 1 F). Mass spectrum (EI) m/z 152 (M^+, 33%), 150 (M^+, 100). Accurate mass spectrum (EI) m/z calcd. for $C_4HN_2F_2Cl$, 149.9796; found, 149.9814. **5**: NMR (C_6D_6, 300 K): ^{19}F (470.4 MHz): δ −45.64 (s, 1 F), −55.36 (s, 1 F). Mass spectrum (EI) m/z 278 (M^+, 30%), 276 (M^+, 100).

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